

Q&A: CDC's Clinical Studies of Pre-Exposure Prophylaxis for HIV Prevention



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Research Rationale

Why is CDC launching trials of pre-exposure prophylaxis for HIV prevention?

CDC is sponsoring these trials because safe and effective new approaches to HIV prevention are urgently needed. Worldwide, nearly 11,000 people continue to become infected every day (over four million per year). In the United States alone, an estimated 40,000 people become infected each year. Although behavior change programs have contributed to dramatic reductions in the number of annual infections in the United States and many other nations, far too many people remain at high risk.

With an effective vaccine years away, there is mounting evidence that antiretroviral agents may be able to play an important role in reducing the risk for transmission. Researchers believe that an HIV drug approved by the Food and Drug Administration—tenofovir disoproxil fumarate (tenofovir, brand name Viread) used alone or in combination with emtricitabine (together, known by the brand name Truvada)—taken daily as an oral preventive is among the most important new prevention approaches being investigated today. The approach is called pre-exposure prophylaxis, or PrEP.

If proven safe and effective, PrEP could help address the urgent need for a female-controlled prevention method for women worldwide who are unable, because of cultural and other barriers, to negotiate condom use. Furthermore, if effective, it could provide an additional safety net for all men and women at risk due to sexual or drug-

using behaviors, when combined with reducing the number of sexual partners, HIV counseling and testing, condom use, use of sterile syringes, and other prevention measures.

How would HIV treatment drugs work to protect against HIV infection?

The concept of providing a preventive before exposure to an infectious agent is not new. For example, travelers to an area where malaria is common are advised to take medication before and during travel to prevent the disease. The medicine to prevent illness is then already in their bloodstream if they are exposed to the malaria parasite.

Researchers believe that the same concept may work to protect people from HIV infection. Theoretically, if HIV replication can be inhibited from the moment the virus enters the body, it may not be able to establish a permanent infection.

What data suggest that this approach may be safe and effective?

Several sources of data suggest that an antiretroviral drug, taken regularly, may prove effective in reducing a person's risk for infection:

- Providing a single dose of the antiretroviral drug nevirapine to HIV-infected women during labor and to their newborns immediately after birth has reduced the risk for mother-to-child transmission of HIV about 50%.
- In observational studies, the antiretroviral drug zidovudine, taken soon after exposure and continued for several weeks, has been

associated with an 80% reduction in the risk of HIV infection among health care workers after needlesticks or other accidental exposures.

- Animal studies have shown that tenofovir, administered before and immediately after a single retroviral exposure, can reduce the transmission of a virus similar to HIV in monkeys.
- Finally, an animal study demonstrated that pre-exposure injections with tenofovir plus emtricitabine protected monkeys from multiple exposures to an HIV-like virus.

The safety and efficacy of tenofovir and a tenofovir-emtricitabine combination pill for the treatment of HIV infection has been well established in clinical studies and medical settings. The U.S. Food and Drug Administration (FDA) licensed tenofovir for use as an HIV treatment in adults in October 2001, and licensed the tenofovir-emtricitabine combination pill for use as an HIV treatment in August 2004. Over 150,000 HIV-infected patients around the world have now used these drugs. Among these patients, tenofovir has resulted in a relatively low level of side effects, compared to other HIV treatments. The most common side effects include nausea and vomiting, and loss of appetite. Tenofovir plus emtricitabine has also been associated with a relatively low level of side effects, which include diarrhea, nausea, fatigue, headache, dizziness, and rash.

One of the key objectives of these trials is to determine for certain whether the study drugs are safe and well tolerated by HIV-negative persons; and safety will be closely monitored throughout the trials. Researchers expect side effects to be even less common in the healthy, HIV-negative volunteers in these HIV prevention trials.

Why study two different drugs?

Globally, an estimated 11,000 new HIV infections occur daily. As such, additional prevention approaches are urgently needed. A combination of studies – of both tenofovir alone and tenofovir plus emtricitabine – will allow us to move forward

as quickly and effectively as possible in the search for new solutions.

There are significant data suggesting the promise of both of these HIV treatment drugs. Because we don't yet know for sure how the animal data will correlate to human protection, we believe it is essential to move forward as quickly as possible to evaluate both of these promising interventions.

Trial Designs and Objectives

What specific CDC studies are under way or planned?

CDC is currently sponsoring three separate trials in Thailand, Botswana, and the United States, which together are designed to answer important questions about the safety and efficacy of PrEP for several of the populations now at greatest risk for infection worldwide. In all, these trials will involve 3,200 participants.

- In Thailand, CDC is conducting a trial to determine if once-daily oral tenofovir is safe and effective in reducing HIV transmission among injection drug users (IDUs). The trial is being conducted in collaboration with the Bangkok Metropolitan Administration and the Thailand Ministry of Public Health.
- In Botswana, CDC will be conducting a trial in collaboration with the Botswana Ministry of Health to provide data on the safety and efficacy of a once-daily tenofovir plus emtricitabine pill in reducing transmission among young heterosexual men and women.

The Botswana research will also provide important information on the safety of tenofovir alone in this population. Because the trial had originally planned to study tenofovir alone (before there was evidence to support initiating trials of tenofovir plus emtricitabine), the study had already enrolled 71 high-risk men and women. Researchers will continue to follow these participants to obtain data on the safety of tenofovir alone, until the new trial is initiated.

- In the U.S., CDC is evaluating the safety and tolerability of once-daily tenofovir alone among men who have sex with men (MSM). This trial will not be large enough to evaluate the drug's effectiveness in reducing HIV transmission. It is being conducted in collaboration with the San Francisco Department of Public Health and the AIDS Research Consortium of Atlanta. (Note: The efficacy of a once-daily PrEP regimen among MSM in Peru is being evaluated independently by the National Institutes of Health.)

In addition to the three trials currently under way, CDC is in the planning stages for a separate U.S. study to assess the clinical safety of tenofovir plus emtricitabine in HIV-uninfected persons. Potential sites for this study are still being evaluated.

What other issues will the trials examine?

All three CDC studies are also designed to address several issues that will be critical to the design of future studies, as well as HIV prevention and treatment programs.

Impact on behavior: Understanding the potential impact of use of a daily preventive drug on HIV risk behaviors will be critical should any PrEP drug prove effective in reducing HIV transmission. One of the greatest risks, as efforts progress to identify new biomedical prevention approaches, is that persons at risk for HIV infection will reduce their use of proven behavioral prevention strategies. Because no single prevention strategy will be 100% effective against HIV transmission, reducing transmission will require determining how best to integrate all available prevention strategies—both biomedical and behavioral. During the trials, all participants will receive state-of-the-art HIV risk-reduction counseling and other proven HIV prevention interventions.

Adherence and acceptability: Even if these trials demonstrate that PrEP can reduce HIV transmission, it is critical to understand whether persons at risk will be willing and able to maintain consistent use of a daily drug. These trials will

therefore closely examine participants' adherence to, and acceptance of, daily oral preventive drug use.

Resistance: A key question about resistance will be addressed during the trials. Although resistance to tenofovir is uncommon among HIV-infected persons when used in combination with other drugs, it is unclear how often resistance may develop if prophylaxis fails and persons become infected while taking tenofovir alone. Similarly, while the risk of drug-resistant virus will likely be lower in the tenofovir plus emtricitabine trial, due to the presence of two drugs, it will be important to assess any resistance to either drug that emerges.

Several study procedures have been designed to minimize the risk of resistance among any individuals who become infected despite receiving PrEP. Regular HIV testing with a rapid HIV test and immediate discontinuation of study pills if participants become infected will result in a very low risk of resistant virus emerging. Additionally, HIV resistance testing will be provided to all persons infected during the trial. These data will provide important information on the degree to which resistance occurs and will help guide treatment decisions as infected persons are referred to treatment and care.

When will the trials begin and how are they designed?

The Thailand and U.S. trials of tenofovir began in 2005 and the Botswana trial of tenofovir plus emtricitabine is scheduled to begin in late 2006. All three trials are randomized, double-blind, placebo-controlled trials. In each trial, all participants will receive risk-reduction counseling and other prevention services, including condoms. In addition, half of the participants will be assigned by chance to receive one antiretroviral pill daily (either tenofovir alone or tenofovir plus emtricitabine, depending on the trial site), and the other half will be assigned by chance to take one daily placebo pill (a similar pill without active medication). Neither researchers nor participants

will know a participant's group assignment. This design allows the researchers to determine in a scientifically valid way whether the risks for side effects and HIV infection are different for persons taking the study drug versus persons taking the placebo.

Botswana and Thailand

The trials in Botswana and Thailand are safety and efficacy trials. The Botswana trial is examining the safety and efficacy of tenofovir plus emtricitabine, and the Thailand trial is examining the safety and efficacy of tenofovir.

Botswana: The Botswana trial is being conducted in collaboration with the Botswana government and will enroll 1,200 HIV-negative heterosexual men and women, aged 18–29, in the nation's two largest cities, Gaborone and Francistown. Participants will be recruited at a number of venues, including HIV voluntary counseling and testing centers, sexually transmitted disease and family planning clinics, youth organizations, and community events.

Thailand: The Thailand trial is being conducted in collaboration with the Bangkok Metropolitan Administration and the Thailand Ministry of Public Health and is enrolling 1,600 HIV-negative injection drug users (IDUs) at 17 drug-treatment clinics in Bangkok. Participants will be recruited at the drug treatment clinics, at community outreach sites, and through a peer referral program.

United States

The U.S. trial is designed to assess the clinical and behavioral safety of once-daily tenofovir among HIV-negative men who have sex with men (MSM). The trial is being conducted at two sites in collaboration with the San Francisco Department of Public Health and the AIDS Research Consortium of Atlanta. A variety of previously successful recruitment techniques, including outreach and referrals through clinician and community-based service organizations, will be used to enroll 400 HIV-negative MSM who

report having had anal intercourse during the past 12 months. To reflect the demographics of the U.S. HIV epidemic, a substantial proportion of participants will be MSM of color.

Participants will be randomly assigned to one of four study groups. Two groups will receive either tenofovir or placebo immediately; the other two groups will receive either tenofovir or placebo 9 months after enrollment. This design will allow researchers to compare risk behaviors among persons who are and persons who are not taking a daily pill. This analysis will be critical to understanding the potential impact of a daily drug regimen on HIV risk behavior.

Why have these populations been selected to take part in the trials?

It is critical to evaluate new prevention methods among the populations who most urgently need them. These and other studies of PrEP will determine if the strategy is safe and effective in reducing transmission among individuals at highest risk for HIV infection around the world.

Botswana has one of the most widespread HIV epidemics in the world: an estimated 31% of the population 15–49 years of age are infected. Data suggest that new infections are increasing most rapidly among young heterosexual men and women. It is estimated that 24% of sexually active women aged 18–19 are infected with HIV and that almost 40% of those aged 20–24 are infected. Among men, the peak seems to occur later: 11% of men aged 20–24 and 28% of men aged 25–29 are believed to be HIV infected. These data suggest very high incidence among young men and women.

In Thailand, HIV prevalence is high among injection drug users (IDUs): an estimated 42% of IDUs are already infected. As a result of the extensive risk reduction counseling and other prevention services provided, HIV incidence among IDUs participating in research trials in the Bangkok drug treatment clinics has declined by

over 50% since 1996. Still, a recent study found that HIV incidence among Thai IDUs was over 3% per year. Given estimates of the number of IDUs in Bangkok, this means that approximately 750 men and women in the city become infected through this transmission route every year.

In the United States, MSM continue to be at the greatest risk for HIV infection. Recent data from the 33 states with long-standing HIV reporting systems indicate that during 2001–2004, MSM accounted for 44% of new HIV diagnoses. Of the roughly one million people living with HIV in the U.S., an estimated 45% are MSM. Additionally, a recent five-city study of HIV prevalence among MSM found that 25% of MSM overall, and 46% of black MSM, were infected in those cities.

Who will be eligible to participate in the PrEP trials?

Because the trials are designed to determine the safety and efficacy of PrEP as an HIV prevention strategy, all participants will be healthy and HIV-negative. To protect the health of participants and ensure that trial data are accurate, several conditions would render some persons ineligible for participation. These include the ongoing use of prescription medication, pregnancy or breast feeding, a history of kidney or bone disease, and participation in any other HIV clinical trial. Additional conditions, including active, untreated syphilis, hypertension, and alcohol or substance use, may also prevent some MSM from participating in the U.S. trial.

Are similar trials being conducted elsewhere?

Yes. Family Health International, with funding from the Bill and Melinda Gates Foundation, has completed a similar trial of tenofovir for HIV prevention among young women in Ghana. That trial will soon provide important data on the safety and acceptability of a once-daily PrEP regimen. The National Institutes of Health will be conducting a PrEP safety and efficacy trial among MSM in Peru.

What is the cost of the CDC studies of PrEP?

CDC funding of all three PrEP trials will total \$23 million over 6 years.

For the Botswana trial, CDC will provide a total of \$10 million in support. In Thailand, CDC's contribution will be \$9 million, and in the United States, CDC will provide \$4 million to the two institutions conducting the trial.

Safeguards and Services for Trial Participants

What safeguards are in place to ensure protection of the volunteers?

To ensure that each of these trials remains on a solid scientific and ethical foundation, all procedures and plans are reviewed and approved by scientific and ethical review committees at CDC (called institutional review boards, or IRBs), as well as by IRBs established by each host country and research site. Additionally, data on safety, enrollment, and efficacy will be reviewed at standard intervals by an independent data safety and monitoring board (DSMB) for the Botswana and Thai trials and by an independent safety review committee for the U.S. trial. These committees review emerging data to ensure that continuing the trial is safe and to determine the point at which the results are conclusive. If scientific questions arise during the trials, these committees will meet more frequently.

Will trial participants increase their risk behavior when they begin taking daily pills?

Several critical steps are being taken to guard against this possibility. First, it is important to ensure that participants understand that trial participation may not protect them from HIV infection—because they may receive a placebo, or they may receive the study drug, the efficacy of which remains unproven. This and other key

aspects of the trial, including potential risks and benefits of participation, are explained to potential volunteers in depth in language they understand, prior to their enrollment. To ensure participants fully understand all aspects of their participation, all volunteers will be required to pass a comprehension test prior to providing written informed consent.

Second, to assist participants in eliminating or reducing HIV risk behaviors, extensive counseling will be provided at each study visit, and more often if needed. The interactive counseling to be provided has been proven to reduce the risk of HIV and other STDs in multiple populations, including past participants of similar trials. Participants will also be offered free condoms and STD testing and treatment to reduce their risk for HIV infection. Additionally, injection drug users will be referred to, and/or offered follow-up in, a methadone treatment program and will receive bleach and instructions on how to use it to clean needles. Consistent with Thai government policy, sterile syringes will not be provided, but are widely available in Thailand without a prescription and at low cost (one sterile syringe and one needle cost about 5 Thai baht, or about \$0.12).

How will CDC evaluate the impact of PrEP if participants reduce their risk behavior?

Although participants will likely be at lower risk for infection because of the prevention services received during the trial, the design of the trial will enable CDC to distinguish between the impact of these services and the impact of the study drugs. Because all participants will receive equivalent prevention services but only half will be given the study drugs, any difference in the rate of HIV infection between the two groups should be due to the study drugs.

What will happen to participants who do become infected during the trial?

Despite optimal prevention counseling, some participants will become HIV infected during the trial. To ensure that infected participants are

quickly referred to the best available medical and psychosocial services, they will receive free rapid HIV testing at every visit. Participants who become infected will receive confirmatory testing for infection, post-test risk-reduction and support counseling, as well as help enrolling in local HIV care programs. Both Thailand and Botswana have antiretroviral treatment and HIV care programs in place at minimal or no cost to patients. In the United States, participants will be referred to local health care providers or public programs for needed medical and social services.

To help guide treatment decisions and to determine whether prior exposure to tenofovir or tenofovir plus emtricitabine affects the course of disease, testing will be provided for viral load, CD4 count, and HIV resistance mutations, and infected participants will be followed up for an additional 12 months.

What are the most common side effects associated with the drugs being tested?

These trials will be among the first to evaluate the safety of tenofovir alone and tenofovir plus emtricitabine in HIV-negative persons. However, among HIV-positive persons who have taken tenofovir in combination with other antiretroviral drugs, the most common side effects are nausea, vomiting, and loss of appetite. There have also been reports of uncommon, but more serious effects, such as impaired kidney function or reductions in bone density. These effects have largely been reversible when the person stopped taking the drug.

Tenofovir plus emtricitabine has also been associated with a relatively low level of side-effects, which include diarrhea, nausea, fatigue, headache, dizziness, and rash. There have been infrequent reports of more serious side effects, including impaired kidney function and lactic acidosis (a build-up of lactic acid in the blood). As with tenofovir, these effects have largely been reversed after use of the drug was discontinued.

Laboratory testing will be used to carefully monitor all participants for signs of these conditions so that the study drugs can be stopped immediately should problems be identified. Researchers anticipate that healthy, HIV-negative participants will experience fewer side effects than do HIV-infected populations taking multiple medications.

Will health care be provided for any health problems related to the drugs?

In all three trials, researchers will monitor participants closely for drug-related side effects. If problems requiring treatment occur, participants will be quickly linked to needed medical care. Care systems differ by country.

In Botswana, the government will provide any needed medical care through the national health care system. In the United States, participants will access needed care through private health insurance or if uninsured, will be provided facilitated referrals to public health care providers. In Thailand, care will be provided in local government clinics.

Community Involvement in These Studies

What is being done to solicit input from the communities in which these trials will be conducted?

CDC will continue to work closely with community partners at each research site to ensure active community participation during the planning and implementation of these trials.

Botswana: In Botswana, community advisory boards have been established at each site. The boards comprise representatives from local governments (elected and traditional), as well as community members and representatives from key stakeholder organizations. These groups will provide input to researchers throughout the trial. Additionally, community liaisons at each site

conduct outreach to community organizations and respond to any questions or concerns. Participant advisory boards will also be set up when the trial begins.

Thailand: In Thailand, a community relations committee, composed of injection drug users from each of the 17 drug treatment clinics, family members, and representatives of local community organizations, meets regularly and provides advice to trial staff on all aspects of trial design and implementation. Additionally, a community liaison serves as a bridge between researchers and community organizations, responding to questions or concerns throughout the trial.

United States: In the United States, both sites have established active community advisory boards that are consulted regularly about trial procedures and educational materials for potential participants. Members of these boards will provide advice throughout the trials. Community educators at each site work to ensure that community organizations are updated on trial progress and to respond to questions or concerns.

In addition to the regular input received by these established committees, broader outreach and consultations with advocates and community-based organizations representing populations at risk for HIV have been, and will continue to be, held, as needed, to address plans for HIV prevention research and programs.

Anticipated Results and Impact

When will the results of the trials be available?

As eager as we are for data about this new approach for HIV prevention, results of the trial won't be available until sufficient data have been collected and analyzed to determine whether the drugs are safe and effective. We are probably a year to three years away from trial results. Independent panels of experts will monitor the trials closely so that the trials can be concluded as soon as definitive answers are available.

If PrEP does prove to be effective at preventing HIV infection in this trial, how will the drugs be made available to people who need or want it?

If the efficacy trials in Botswana and Thailand prove that one or both PrEP drugs are effective, participants in these trials and their communities will be the first to benefit. All trial participants will receive the appropriate drugs immediately and will continue to receive it for one year while CDC works with the Botswana Drugs Regulatory Unit and/or the Thai Food and Drug Administration for approval of use by the health care systems in these countries.

CDC is also working to determine how possible trial outcomes will influence future HIV prevention research, policy, and programs in the United States and worldwide. CDC will collaborate with its partners in the Department of Health and Human Services, the State Department, the Food and Drug Administration, and the World Health Organization to determine how to most effectively apply various potential results from these trials to real-world practice.

If the drugs prove safe and effective in one population, will they work equally well in other populations?

CDC is conducting studies in different populations to help address this question. In general, HIV is more readily transmitted through injection drug use than through sexual exposure and more easily transmitted during rectal intercourse than during vaginal intercourse. However, the correlates of protection for various modes of transmission are not fully understood. It is therefore not known what level of antiretroviral drug activity at which sites (e.g., in the blood, the vaginal mucosa, or the rectal mucosa) will be needed to interrupt transmission. For these reasons, the efficacy of particular drugs in reducing HIV transmission in one population may not necessarily apply to other at-risk populations.

If studies show that PrEP reduces the risk of HIV transmission, will people still have to practice other risk-reduction behaviors for HIV?

Yes. Regardless of the outcome, CDC will not recommend PrEP as a first-line defense against HIV infection. Abstinence and mutual monogamy with an HIV-negative partner will remain the only 100% effective ways to prevent infection. However, if effective, this strategy could provide an additional safety net to sexually active persons at risk, when combined with reduction in the number of sexual partners, HIV counseling and testing, consistent and correct condom use, and other prevention strategies.

It is also important to remember that taking PrEP drugs will not prevent acquisition of syphilis, gonorrhea, chlamydia, herpes, hepatitis, or other sexually transmitted diseases, many of which play a role in facilitating HIV transmission or speeding HIV disease progression.

Will support for these trials take away funding from behavioral interventions?

Absolutely not. As we move forward with our search for new prevention strategies, it will be critical to determine how the approaches that are proven effective can best be integrated into programs. Effective behavior-change programs have greatly reduced the rate of HIV infection in the United States, and many other nations during the past 2 decades of the HIV epidemic. Because no strategy will be 100% effective in preventing HIV infection, their future impact will ultimately be determined by how effectively strategies are used in combination to provide the greatest protection to individuals at risk.

Are physicians in certain places already prescribing the drugs being studied for HIV prevention?

According to media reports, a small number of physicians in the United States and the United Kingdom are already prescribing PrEP in hopes

of preventing HIV infection among patients in their practices. But individuals who take HIV medications before engaging in high-risk behavior to avoid infection are doing so in the absence of clinical data demonstrating that the drugs are safe and effective, and at potentially serious risk. This is especially true if they are using the drugs instead of, rather than in addition to, existing prevention methods.

That is why CDC is conducting these important trials—to contribute to the work of scientifically evaluating the safety and efficacy of PrEP among persons who are at risk. The trials will answer important questions about the impact of a daily pill on risk behavior and help us to determine how PrEP, if effective, can be used in combination with other proven strategies.

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